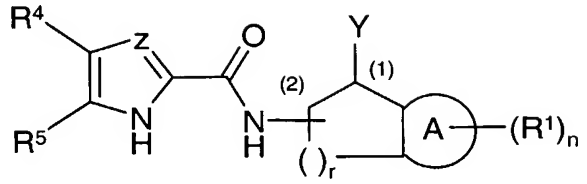
Claims

1. A compound of formula (1):



(1)

wherein:

Z is CH or nitrogen;

R^4 and R^5 together are either –S-C(R^6)=C(R^7)- or –C(R^7)=C(R^6)-S- ;

R^6 and R^7 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy and (1-4C)alkanoyl;

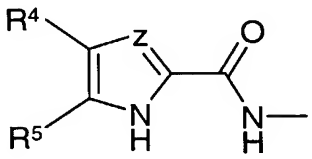
A is phenylene or heteroarylene;

n is 0, 1 or 2;

R^1 is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, *N*-(1-4C)alkylcarbamoyl, *N*,*N*-((1-4C)alkyl)$_2$carbamoyl, sulphamoyl, *N*-(1-4C)alkylsulphamoyl, *N*,*N*-((1-4C)alkyl)$_2$sulphamoyl, -S(O)$_b$(1-4C)alkyl (wherein b is 0,1,or 2), -OS(O)$_2$(1-4C)alkyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkanoyloxy, hydroxy(1-4C)alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy and –NHSO$_2$(1-4C)alkyl;

or, when n is 2, the two R^1 groups, together with the carbon atoms of A to which they are attached, may form a 4 to 7 membered saturated ring, optionally containing 1 or 2 heteroatoms independently selected from O, S and N, and optionally being substituted by one or two methyl groups;

r is 1 or 2; and when r is 1 the group



is a substituent on carbon (2) and when r is 2 (hereby forming a six membered ring) the same group is a substituent on carbon (2) or on carbon (3);

Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, -(1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, $-C=NR^2$, (1-4C)alkoxy, aryloxy, heterocyclyloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, $-NHOHC(=O)R^2$, $-SO_2NR^2R^3$, $-N(R^2)SO_2R^2$, aryl and heterocyclyl], -C(O)NOH, -C(O)NSH, -C(N)OH, -C(N)SH, $-SO_2H$, $-SO_3H$, $-SO_2N(OH)R^2$, -(2-4C)alkenyl, $-SO_2NR^2R^3$, -(1-4C)alkylC(O)R^2, -(1-4C)alkylC(O)OR^2, -(1-4C)alkylSC(O)R^2, -(1-4C)alkylOC(O)R^2, - (1-4C)alkylC(O)NR^2R^3 , -(1-4C)alkylOC(O)OR^2, -(1-4C)alkyl$N(R^2)$C(O)OR^2, -(1-4C)alkyl$N(R^2)$C(O)NR^2R^3, -(1-4C)alkylOC(O)NR^2R^3, (3-6C)cycloalkyl (optionally substituted by 1 or 2 R^8), aryl, heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom), -(1-4C)alkylSO_2(2-4C)alkenyl and $-S(O)_cR^2$ (wherein c is 0, 1 or 2);

R^2 and R^3 are independently selected from hydrogen, -O(1-4C)alkyl, -S(1-4C)alkyl, -N(1-4C)alkyl, heterocyclyl, aryl, and (1-4C)alkyl [optionally substituted by 1 or 2 R^8 groups];

or

wherein NR^2R^3 may form a 4 to 7 membered saturated, partially saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S (provided there are no O-O, O-S or S-S bonds), wherein any $-CH_2-$ may optionally be replaced by –C(=O)-, and any N or S atom may optionally be oxidised to form an N-oxide or SO or SO_2 group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, (1-4C)alkyl, hydroxy, (1-4C)alkoxy and (1-4C)alkyl$S(O)_b$- (wherein b is 0, 1 or 2);

R^8 is independently selected from hydrogen, hydroxy, (1-4C)alkyl, (2-4C)alkenyl, (1-4C)alkoxy, cyano((1-4C))alkyl, amino((1-4C))alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from (1-4C)alkyl, hydroxy, hydroxy((1-4C))alkyl, dihydroxy((1-4C))alkyl, $-CO_2$(1-4C)alkyl, aryl and aryl((1-4C))alkyl], halo((1-4C))alkyl, dihalo((1-4C))alkyl, trihalo((1-4C))alkyl, hydroxy((1-4C))alkyl, dihydroxy((1-4C))alkyl, (1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, aryl, heterocyclyl, (heterocyclyl)(1-4C)alkyl, (3-7C)cycloalkyl (optionally substituted with 1 or 2 hydroxy groups, (1-4C)alkyl or $-CO_2$(1-4C)alkyl), (1-4C)alkanoyl, (1-4C)alkyl$S(O)_b$- (wherein b is 0, 1 or 2), (3-6C)cycloalkyl$S(O)_b$- (wherein b is 0, 1 or 2), aryl$S(O)_b$- (wherein b is 0, 1 or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1 or 2), benzyl$S(O)_b$- (wherein b is 0, 1 or 2),

(1-4C)alkylS(O)$_c$(1-4C)alkyl- (wherein c is 0, 1 or 2), -N(OH)CHO, -C(=N-OH)NH$_2$, -C(=N-OH)NH(1-4C)alkyl, -C(=N-OH)N((1-4C)alkyl)$_2$, -C(=N-OH)NH(3-6C)cycloalkyl, -C(=N-OH)N((3-6C)cycloalkyl)$_2$, -COCOOR^9, -C(O)N(R^9)(R^{10}), -NHC(O)R^9, -C(O)NHSO$_2$((1-4C)alkyl), -NHSO$_2$R^9, (R^9)(R^{10})NSO$_2$-, -COCH$_2$OR^{11}, -COCH$_2$OH, (R^9)(R^{10})N- , -COOR^9, -CH$_2$OR^9, –CH$_2$COOR^9 , –CH$_2$OCOR^9, -CH$_2$CH(CO$_2$R^9)OH, –CH$_2$C(O)NR^{9}R^{10}, -(CH$_2$)$_w$CH(NR^{9}R^{10})CO$_2$R$^{9'}$ (wherein w is 1, 2 or 3), and -(CH$_2$)$_w$CH(NR^{9}R^{10})CO(NR$^{9'}$R$^{10'}$) (wherein w is 1, 2 or 3) ;

R^9 , R$^{9'}$, R^{10} and R$^{10'}$ are independently selected from hydrogen, hydroxy, (1-4C)alkyl (optionally substituted by 1 or 2 R^{11}), (2-4C)alkenyl, (3-7C)cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), cyano((1-4C))alkyl, trihaloalkyl, aryl, heterocyclyl, heterocyclyl((1-4C)alkyl), -CO$_2$(1-4C)alkyl; or

R^9 and R^{10} together with the nitrogen to which they are attached, and/or R$^{9'}$ and R$^{10'}$ together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl, (1-4C)alkoxy and heterocyclyl; or the ring may be optionally substituted on two adjacent carbons by –O-CH$_2$-O- to form a cyclic acetal wherein one or both of the hydrogens of the -O-CH$_2$-O- group may be replaced by a methyl;

R^{11} is independently selected from (1-4C)alkyl and hydroxy(1-4C)alkyl;

or a pharmaceutically acceptable salt or pro-drug thereof.

2. A compound of the formula (1), or a pharmaceutically acceptable salt or pro-drug thereof, as claimed in claim 1, wherein A is phenylene.

3. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1 or claim 2, wherein n is 0.

4 A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of the preceding claims wherein r is 1.

5. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of the preceding claims wherein R^6 and R^7 are independently hydrogen or halo.

6. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of the preceding claims wherein Y is selected from $-C(O)OR^2$, $-C(O)NR^2R^3$, -(1-4C)alkyl [optionally substituted by a substituent selected from hydroxy, (1-4C)alkoxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-NR^2C(=O)R^2$ and $-SO_2NR^2R^3$], -(1-4C)alkylC(O)R^2, -(1-4C)alkylC(O)OR^2, -(1-4C)alkylOC(O)R^2, - (1-4C)alkylC(O)NR^2R^3, -(1-4C)alkylOC(O)OR^2, -(1-4C)alkylN(R^2)C(O)OR^2, -(1-4C)alkylN(R^2)C(O)NR^2R^3, -(1-4C)alkylSC(O)R^2, -(1-4C)alkylOC(O)NR^2R^3, -(1-4C)alkylSO_2(2-4C)alkenyl and $-SO_cR^2$ (wherein c is 0, 1 or 2).

7. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of the preceding claims wherein R^2 and R^3 are independently selected from hydrogen, heterocyclyl, -O(1-4C)alkyl, -N(1-4C)alkyl, (1-4C)alkyl [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from chloro, fluoro, hydroxy and methoxy.

8. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of the preceding claims wherein R^8 is independently selected from hydrogen, hydroxy, -C(O)N(R^9)(R^{10}), -NHC(O)R^9, -COOR^9, $-CH_2OR^9$, $-CH_2COOR^9$, $-CH_2OCOR^9$, aryl, heterocyclyl, and 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof.

9. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of the preceding claims wherein R^9 and R^{10} are independently selected from hydrogen, hydroxy and (1-4C)alkyl) or R^9 and R^{10} together with the nitrogen to which they are attached form a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring.

10. A pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

11. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, for use in a method of treatment of a warm-blooded animal such as man by therapy.

12. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, for use as a medicament.

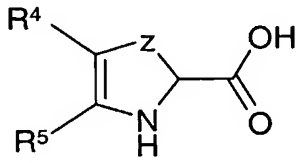
13. A compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in claim 1, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

14. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

15. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

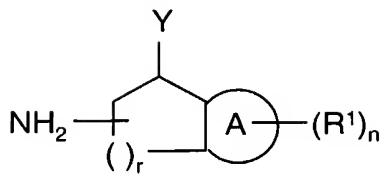
16. A process for the preparation of a compound of formula (1) as claimed in claim 1, which process comprises:

reacting an acid of the formula (2):



(2)

or an activated derivative thereof; with an amine of formula (3):



(3)

and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.